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Geographic altitude and prevalence of underweight, stunting and wasting in newborns with the INTERGROWTH-21st standard☆

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Fetal growth retardation;
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Abstract
Objective: To assess the prevalence and risks of underweight, stunting and wasting by gestational age in newborns of the Jujuy Province, Argentina at different altitude levels.
Methods: Live newborns (n = 48,656) born from 2009–2014 in public facilities with a gestational age between 24^{+0} to 42^{+6} weeks. Phenotypes of underweight (<P3 weight/age), stunting (<P3 length/age) and wasting (<P3 body mass index/age) were calculated using INTERGROWTH-21st standards. Risk factors were maternal age, education, body mass index, parity, diabetes, hypertension, preeclampsia, tuberculosis, prematurity, and congenital malformations. Data were grouped by the geographic altitude: ≥2000 or <2000 m.a.s.l. Chi-squared test and a multivariate logistic regression analysis were performed to estimate the risk of the phenotypes associated with an altitudinal level ≥2000 m.a.s.l.
Results: The prevalence of underweight, stunting and wasting were 1.27%, 3.39% and 4.68%, respectively, and significantly higher at >2000 m.a.s.l. Maternal age, body mass index >35 kg/m^2, hypertension, congenital malformations, and prematurity were more strongly associated with underweight rather than stunting or wasting at ≥2000 m.a.s.l.

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Conclusions: Underweight, stunting, and wasting risks were higher at a higher altitude, and were associated with recognized maternal and fetal conditions. The use of those three phenotypes will help prioritize preventive interventions and focus the management of fetal undernutrition.

PALAVRAS-CHAVE
Retardo do crescimento fetal;
Recém-nascido;
Peso ao nascer;
Prematuridade;
Malformações

Altitude geográfica e prevalência de recém-nascidos abaixo do peso, com baixa estatura e emaciação de acordo com o padrão do Projeto Consórcio Internacional de Crescimento Fetal e Neonatal para o Século XXI (INTERGROWTH-21st)

Resumo
Objetivo: Avaliar a prevalência e os riscos de recém-nascidos abaixo do peso, baixa estatura e emaciação por idade gestacional da Província de Jujuy, Argentina, em diferentes níveis de altitude.
Métodos: Recém-nascidos vivos (n = 48.656) nascidos entre 2009 e 2014 em instalações públicas entre 24^{+0}-42^{+6} semanas de idade gestacional. Os fenótipos de abaixo do peso (< P3 peso/idade), baixa estatura (< P3 comprimento/idade) e emaciação (< P3 índice de massa corporal/idade) foram calculados utilizando os padrões do INTERGROWTH-21st. Os fatores de risco foram idade materna, escolaridade, índice de massa corporal, paridade, diabetes, hipertensão, pré-eclâmpsia, tuberculose, prematuridade e malformações congênitas. Os dados foram agrupados pela altitude geográfica: $\geq$ 2000 ou < 2000 m.a.s.l. O teste qui-quadrado e a análise de regressão logística multivariada foram realizados para estimar o risco dos fenótipos associados ao nível de altitude $\geq$ 2000 m.a.s.l.
Resultados: A prevalência de abaixo do peso, baixa estatura e emaciação foram 1,27%, 3,39% e 4,68%, respectivamente, significativamente maiores em > 2000 m.a.s.l. A idade materna, índice de massa corporal > 35 kg/m^2, hipertensão, malformações congênitas e prematuridade foram mais fortemente associados a abaixo do peso e não baixa estatura ou emaciação em $\geq$2000 m.a.s.l.
Conclusões: Os riscos de abaixo do peso, baixa estatura e emaciação foram maiores em altitude mais elevada e foram associados a condições maternas e fetais reconhecidas. O uso desses três fenótipos ajudará a priorizar as intervenções preventivas e focar no manejo da desnutrição fetal.

Introduction

Several anthropometric measures are widely used by neonatologists to assess newborn nutrition, such as low birth weight (<2500 g), small for gestational age (SGA, birth weight [BW] below 10th percentile for gestational age [GA]), Ponderal Index[1] (PI, weight/length^3), proportionality (estimated by z-transformation of PI)[2] and placental insufficiency[3] However, none is synonymous with intrauterine growth restriction.[4]

Neonatal anthropometry is characterized by being inexact and by the lack of validation and consensus of its available indexes.[5] In addition, there is no correspondence and harmonization between the different criteria to assess pre- and postnatal nutritional status for constant and continuous growth monitoring in the different stages of ontogenesis.[6]

The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st Project – IG-21) recently published the standards for newborn weight, length and head circumference.[7] It is a cross-sectional, multicenter study on size at birth by sex and GA, conducted with the same prescriptive approach and methodological design as those used in establishing WHO standards.[8] IG-21 suggests that low weight at a given GA may result from *stunting* (short length for age, reflecting linear growth restriction), *wasting* (low weight for length, or low body mass index [BMI] for age, often reflecting recent weight loss), or both phenotypes. Those are two distinct phenotypes, with different timing and duration of causal insults, specific risk factors, and varied distributions across populations and different prognoses.[9]

Several anthropometry studies on children and adolescents from altitude ecosystems indicate that this population, compared to those living closer to sea level, is shorter and lighter.[10,11] Particularly in newborn infants of Jujuy, birth weight, as well as the indicators of severe intrauterine growth impairment are independently associated with geographic altitude.[2,12–15] However, most studies of altitude effect on fetal growth are limited to term newborn infants.

The objective was to use the IG-21 standard to assess the prevalence and common risks factors of underweight, stunting, and wasting by gestational age (GA) in newborn infants of Jujuy associated with high altitudinal levels.

Material and methods

Study population

This was an observational, analytical, and retrospective study conducted on consecutive births registered by the Perinatal Informatics System (SIP, Ministry of Health of the Province of Jujuy, Argentina) between 2009 and 2014. Exclusion criteria were (1) GA <24^{+0} and >42^{+6} weeks; (2) lack of data on weight, height, GA, sex, and maternal place of residence during pregnancy; (3) twin pregnancy. Alexander's criterion was applied to correct incompatibilities between birth weight and gestational age.[16]

Data assessment

Data were grouped according to geographic altitude of the maternal place of residence into a low altitude (LA) group (<2000 m.a.s.l.) and a high altitude (HA) group (≥2000 m.a.s.l.). Newborn nutritional status was determined with IG-21 standard, using the following phenotypes at birth: (a) Stunting (<3rd percentile length/GA); (b) Wasting (<3rd percentile BMI [Kg/m^2]/GA),[9] and (c) a third phenotype – not included in the IG-21 standard –, *underweight* (BW <3rd percentile for age and sex), indicating a severe insult. This eliminates the chance of erroneous inclusion of a normal newborn in the lower BW distribution. Because the IG-21 Project does not provide an assessment of BMI below 33^{+0} weeks GA, the current study's data included underweight and stunting between 24^{+0} and 42^{+6} weeks, and wasting between 33^{+0} and 42^{+6} weeks.

The following characteristics were analyzed: (1) maternal biological and sociodemographic characteristics: age (<20, 20–24, 25–29, 30–35 and ≥35 years), parity (0, 1, 2 and ≥3), BMI (<18.5 undernutrition; 18.5–24.9 normal nutrition; 25.0–29.9 overweight; 30–34.9 obesity type I; and ≥35 kg/m^2 obesity type II), and education (<8; 8–11 and ≥12 years); (2) diabetes, hypertension, preeclampsia and tuberculosis during pregnancy; and (3) sex, prematurity (<37^{+0} weeks) and congenital malformations for the newborns. Maternal biological and sociodemographic variables were categorical; the remainder were dichotomous.

Statistical analysis

Prevalence of the different phenotypes was estimated by proportion (95% CI [confidence interval]), whereas population differences were analyzed with a chi-squared test and univariate risk: odds ratio (OR and 95% CI). A multivariate logistic regression analysis was performed to estimate the risk of underweight, stunting, and wasting associated with altitude level (exposure variable), and adjusted for maternal age, educational level, BMI, parity, tuberculosis, diabetes, hypertension, preeclampsia, sex, prematurity, and congenital malformations. Low altitude was the reference. Goodness of fit was tested with the Hosmer–Lemeshow test. SPSS (Version 22) and Stata (Version 11) statistical software were used. The statistical level was set at $p < 0.05$.

Ethical issues

The Provincial Committee of Ethics of research in health of Jujuy, Argentina, approved this study.

Results

Between 2009 and 2014, 79,504 live infants were born in the Jujuy Province; 57,471 were registered by SIP. After applying the selection criteria, 48,656 (84.6%, 95% CI 84.3–84.9) newborns were included in the study; of those, 16.8% (16.5–17.2) came from HA (Supplemental Digital Content [SDC] S1, Fig. 1).

Underweight, stunting and wasting prevalence were 1.27% (1.18–1.38), 3.39% (3.24–3.36), and 4.68% (4.49–4.87), respectively. The stunting plus wasting rate was 0.16% (0.12–0.20). The rate of HA underweight infants was 1.13 times higher (0.80–1.49) than the equivalent LA rate, whereas the rates for stunting and wasting were 2.68 (2.10–3.29) and 5.26 (4.61–5.95) times higher, respectively.

Overall, the HA mothers of underweight newborns showed significantly greater age, higher undernutrition, hypertension, prematurity and congenital malformations, but less overweight and obesity type I than the LA mothers. Pregnancies in the HA group with stunted newborns were independently associated with higher undernutrition, but less obesity type I, while wasting-affected newborns in the HA group showed less normal pregnancy nutrition, obesity type I and prematurity, but higher nulliparity and congenital malformations than the newborns of LA mothers (Table 1).

Mean BW and standard deviation (SD) of the three phenotypes was 2012 g (567) for underweight, 2933 g (635) for stunting and 2767 g (427) for wasting, while in children without nutritional deficit it was 3321 g (531).

Mean GA (SD) was 37.5 (3.9) weeks for underweight, 38.6 (2.1) weeks for stunting and 39.0 (1.3) weeks for wasting. Overall prematurity rate was 9.04% (8.79–9.30): 8.01% at HA and 9.25% at LA ($p < 0.001$).

In the Jujuy Province at HA, the underweight, stunting and wasting risks begin to appear from the 29th, 26th, and 33th weeks of gestation, respectively. The prevalence of underweight and stunting at 24^{+0} to 36^{+6} weeks was higher than at 37^{+0} to 42^{+6} weeks ($p < 0.001$) for HA compared with LA. On the other hand, wasting prevalence at 37^{+0} to 42^{+6} weeks was higher than at 24^{+0} to 36^{+6} weeks at HA compared with LA ($p < 0.001$, data not shown) (SDC S2, S3 and S4, Figs. 2–4).

Crude OR (95% CI) for underweight, stunting and wasting associated with HA were 1.92 (1.63–2.27), 2.21 (1.99–2.45) and 2.39 (2.18–2.62), respectively ($p < 0.001$). After adjustment, a slight risk reduction for stunting and a risk increase for the other phenotypes were found, all statistically significant (SDC S5, Table 1). Goodness of fit models were adequate.

Tables 1–3 show maternal and newborn characteristics according to altitude, and their association (adjusted OR, AOR) with the three phenotypes. For underweight, maternal

Table 1 Prevalence of maternal and newborn characteristics and adjusted risk of underweight according to geographic altitude (Jujuy, Argentina, 2009–2014).

Variable		LA (n = 40,442)			HA (n = 8214)			AOR (95% CI)[a]
		Total[b]	n	%	Total[b]	n	%	
Maternal educational level (ys)	<8	1744	30	1.7	305	10	3.3	1.61 (0.97–2.67)
	8–11	1022	16	1.5	466	10	2.1	1.19 (0.64–2.23)
	≥12	37,172	458	1.2	7443	175	2.4	1 (Reference)
Maternal BMI (kg/m^2)	<18.5	1831	23	1.2	276	12	4.3	1.53[c] (1.02–2.30)
	18.5–24.9	19,327	241	1.2	3747	82	2.2	1 (Reference)
	25–29.9	7608	77	1.0	1242	30	2.4	0.69[c] (0.50–0.94)
	30–34.9	2549	23	0.9	286	5	1.7	0.51[c] (0.29–0.92)
	≥35	8623	140	1.6	2663	66	2.5	1.16 (0.62–2.18)
Maternal age (ys)	<20	9006	129	1.4	1981	54	2.7	0.91 (0.61–1.34)
	20–24	11,974	128	1.1	2411	63	2.6	1.04 (0.73–1.47)
	25–29	8896	96	1.1	1812	26	1.4	1 (Reference)
	30–34	6176	79	1.3	1163	34	2.9	1.31 (0.86–1.98)
	≥35	3859	72	1.8	844	18	2.1	1.78[c] (1.13–2.81)
Parity	0	13,616	216	1.6	2851	89	3.1	1.72[c] (1.15–2.56)
	1	10,451	98	0.9	2039	40	2.0	0.98 (0.65–1.46)
	2	6586	65	1.0	1267	19	1.5	0.88 (0.57–1.36)
	≥3	9285	125	1.3	2057	47	2.3	1 (Reference)
TBC	No	39,240	485	1.2	8046	193	2.4	1 (Reference)
	Yes	209	3	1.4	12	0	0.0	0.70 (0.17–9.64)
Diabetes	No	39,207	478	1.2	8062	192	2.4	1 (Reference)
	Yes	128	3	2.3	14	0	0	1.29 (0.95–5.21)
Hypertension	No	38,839	472	1.2	8066	192	2.4	1 (Reference)
	Yes	574	15	2.6	31	1	3.2	2.54[c] (1.14–5.68)
Preeclampsia	No	38,974	476	1.2	8037	189	2.4	1 (Reference)
	Yes	385	9	2.3	45	2	4.4	1.10 (0.33–3.66)
Male	No	19,591	224	1.2	4024	88	2.1	1 (Reference)
	Yes	20,347	260	1.3	3995	107	2.6	1.05 (0.84–1.32)
Congenital malformations	No	29,213	261	0.8	6434	124	1.9	1 (Reference)
	Yes	366	27	7.3	35	6	17.4	7.66[c] (4.83–12.14)
Prematurity	No	37,953	404	0.2	7640	171	0.6	1 (Reference)
	Yes	2489	100	16.1	574	24	25.6	1.54[c] (1.07–2.22)

Hosmer–Lemeshow chi^2 = 4, p = 0.979.
LA, low altitudinal level; HA, high altitudinal level.
Q4 [a] AOR, adjusted OR for all variables of the table.
[b] There were some missing values.
[c] $p < 0.001$.

age greater or equal to 35 years, BMI lower than 18.5 kg/m^2, nulliparity, gestational hypertension, prematurity, and congenital malformations were independently associated with elevated risk at HA. Overweight and obesity type I were associated to lower risk at HA (Table 1).

For stunting, maternal BMI below 18.5 kg/m^2 and congenital malformations were independently associated with higher risk, while BMI of obesity type I showed lower risk (Table 2).

Finally, for wasting, nulliparity and congenital malformations were independently associated with higher risk, while overweight and class I obesity and prematurity were associated with lower risk (Table 3).

Discussion

In the present study, newborns at HA in the Jujuy Province showed a significantly higher risk of underweight, stunting and wasting, and clinical and epidemiologic evidence to support the concept that they are separate anthropometric phenotypes of intrauterine origin is presented. The phenotypes differed in terms of risk factors. As expected, few conditions were associated with similar strength to underweight, stunting and wasting phenotypes; those conditions are mostly recognized as universal risk factors, i.e. GA, maternal undernutrition, obstetric history, and congenital malformations. Other factors, in particular tuberculosis,

Table 2 Prevalence of maternal and newborn characteristics and adjusted risk of stunting, according to geographic altitude (Jujuy, Argentina, 2009–2014).

Variable		LA (n = 40,442)			HA (n = 8214)			AOR (95% CI)[a]
		Total[b]	n	%	Total[b]	n	%	
Maternal educational level (ys)	<8	1691	40	2.4	289	22	7.6	1.02 (0.71–1.48)
	8–11	995	24	2.4	452	20	4.4	1.15 (0.78–1.69)
	≥12	36,468	789	2.2	7202	413	5.7	1 (Reference)
Maternal BMI (kg/m^2)	<18.5	1803	54	3.0	270	21	7.8	1.31[c] (1.01–1.70)
	18.5–24.9	19,008	436	2.3	3628	194	5.3	1 (Reference)
	25–29.9	7425	130	1.8	1203	57	4.7	0.84 (0.71–1.00)
	30–34.9	2493	47	1.9	278	7	2.5	0.71[c] (0.52–0.97)
	≥35	8425	186	2.2	2564	176	6.9	1.03 (0.68–.56)
Maternal Age (ys)	<20	8859	205	2.3	1910	137	7.2	1.02 (0.82–1.28)
	20–24	11,750	266	2.3	2339	128	5.5	1 (Reference)
	25–29	8726	187	2.1	1762	93	5.3	0.93 (0.76–1.13)
	30–34	6041	110	1.8	1113	54	4.9	0.85 (0.66–1.08)
	≥35	3754	84	2.2	816	42	5.1	0.95 (0.72–1.27)
Parity	0	13,387	327	2.4	2749	169	6.1	1 (Reference)
	1	10,238	211	2.1	1983	109	5.5	1.13 (0.89–1.14)
	2	6466	147	2.3	1234	68	5.5	0.99 (0.78–1.25)
	≥3	9063	168	1.9	1977	109	5.5	1.15 (0.91–1.46)
TBC	No	38,008	820	2.2	7786	447	5.7	1 (Reference)
	Yes	204	5	2.5	12	0	0.0	1.21 (0.44–3.32)
Diabetes	No	38,375	1212	3.3	7896	536	7.3	1 (Reference)
	Yes	121	4		15	1	0	0.50 (0.07–3.69)
Hypertension	No	37,636	809	2.1	7808	445	5.7	1 (Reference)
	Yes	545	18	3.3	29	0	0.0	1.21 (0.65–2.27)
Preeclampsia	No	37,770	808	2.1	7778	440	5.7	1 (Reference)
	Yes	362	15	4.1	45	3	6.7	1.30 (0.65–2.59)
Male	No	18,801	624	3.2	3736	295	7.3	1 (Reference)
	Yes	19,500	642	3.2	3752	253	6.3	0.87 (0.76–1.00)
Congenital malformations	No	28,954	820	2.8	6365	352	5.5	1 (Reference)
	Yes	355	29	8.1	33	6	18.2	2.60[c] (1.67–4.06)
Prematurity	No	37,397	981	2.6	7519	445	5.9	1 (Reference)
	Yes	2170	285	13.3	517	103	19.9	1.23 (0.97–1.58)

Hosmer–Lemeshow chi^2 = 4.25, p = 0.833.
LA, low altitudinal level; HA, high altitudinal level.
[a] Adjusted OR for all variables of the table.
[b] There were some missing values.
[c] p < 0.001.

have such a wide range of severity, presentations, and timing during pregnancy that they are not phenotype-specific. On the other hand, overweight and type I obesity showed between 30% and 50% risk reduction for the three phenotypes (a well-described effect that is due to increased birth weight and fat deposition).

No comparable local records exist on the prevalence of nutritional phenotypes in newborns evaluated for GA using IG-21, except for the underweight phenotype.[17] It is worth noting that, in this study,[17] the prevalence of underweight calculated from birth certificates in 2013 in the Argentine Northeast, where the Jujuy Province is located, was similar to the one detected in this study in term newborns. Argentine records on the prevalence of those phenotypes refer to child populations over the age of 6 months calculated with the WHO standard.[18] The National Nutrition and Health Survey (Encuesta Nacional de Nutrición y Salud) performed in Argentina in 2004–2005 establishes, for the population of Jujuy, regardless of the geographic altitude, 1.8% (95% CI 0.8–4.1), 9.5% (95% CI 5.3–16.6) and 0.6% (95% CI 0.3–1.4) prevalence of underweight, stunting and wasting, respectively.[18] A Latin American study[19] compared IG-21 percentiles with newborn Peruvians born >3400 m.a.s.l. and did not find significant differences with reference to the IG-21 standard, but underweight, stunting and wasting prevalence were not estimated.

Table 3 Prevalence of maternal and newborn characteristics and adjusted risk of wasting according to geographic altitude (Jujuy, Argentina, 2009–2014).

Variable		LA (n = 40,442)			HA (n = 8214)			AOR (95% CI)[a]
		Total[b]	n	%	Total[b]	n	%	
Maternal educational level (ys)	<8	1677	82	4.9	289	11	3.8	1.03 (0.75–1.41)
	8–11	989	40	4.0	447	49	11.0	1.16 (0.85–1.59)
	≥12	36,165	1493	4.1	7194	687	9.5	1 (Reference)
Maternal BMI (kg/m^2)	<18.5	1781	94	5.3	269	34	12.6	1.23 (0.99–1.53)
	18.5–24.9	18,907	847	4.5	3636	365	10.0	1 (Reference)
	25–29.9	7398	247	3.3	1209	89	7.4	0.71[c] (0.61–0.83)
	30–34.9	2480	83	3.3	273	24	8.8	0.76[c] (0.59–0.98)
	≥35	8265	344	4.2	2543	235	9.2	0.68 (0.44–1.03)
Age (ys)	<20	8741	447	5.1	1903	196	10.3	0.91 (0.75–1.09)
	20–24	11,669	475	4.1	2342	233	9.9	0.99 (0.84–1.17)
	25–29	8703	330	3.8	1754	139	7.9	1 (Reference)
	30–34	5994	226	3.8	1123	102	9.1	1.02 (0.83–1.25)
	≥35	3698	137	3.7	805	77	9.6	1.16 (0.91–1.48)
Parity	0	13,268	728	5.5	2747	320	11.6	1.64[c] (1.35–2.01)
	1	10,146	383	3.8	1972	176	8.9	1.24 (0.97–1.44)
	2	6415	211	3.3	1239	84	6.8	0.18 (0.79–1.17)
	≥3	9002	293	3.3	1972	167	8.5	0.89 (0.72–1.11)
TBC	No	37,685	1564	4.2	7774	739	9.5	1 (Reference)
	Yes	204	12	5.9	12	1	8.3	1.74 (0.90–3.32)
Diabetes	No	37,332	1557	4.2	7797	742	9.5	1 (Reference)
	Yes	526	20	3.8	27	1	3.7	0.97 (0.50–1.85)
Hypertension	No	37,455	1561	4.2	7767	736	9.5	1 (Reference)
	Yes	354	11	3.1	44	5	11.4	0.95 (0.46–1.96)
Preeclampsia	No	18,305	791	4.1	3607	378	9.5	1 (Reference)
	Yes	18,911	824	4.2	3576	369	9.4	0.95 (0.46–1.96)
Male	No	18,305	791	4.1	3607	378	9.5	1 (Reference)
	Yes	18,911	824	4.2	3576	369	9.4	0.92 (0.83–1.03)
Congenital malformations	No	28,610	11,457	4.0	6310	654	10.3	1 (Reference)
	Yes	335	29	8.7	32	8	25	2.52[c] (1.69–3.75)
Prematurity	No	37,335	1234	3.3	7505	601	8.1	1 (Reference)
	Yes	1496	381	25.4	425	146	34.3	0.64[c] (0.48–0.84)

Hosmer–Lemeshow chi^2 = 1.92, p = 0.983.
LA, low altitudinal level; HA, high altitudinal level.
[a] Adjusted OR for all variables of the table.
[b] There were some missing values.
[c] $p < 0.01$.

The observed prevalences of newborn phenotypes were relatively low, especially for underweight and stunting, because they are also lower than the clinical significance cut-off points <10% and <20%, respectively, suggested by WHO.[20] Stunting at birth seems to have a relatively low prevalence even in low-income settings, but it increases sharply with gestational age.[21] Those results are somewhat similar to an earlier study[9] of fetal growth impairment, which met strict individual eligibility criteria, where stunting affected 3.8% and wasting affected 3.4% of a low-risk population of newborns.

In a recent risk factor analysis for childhood stunting in developing countries, the worldwide leading risk factor was fetal growth restriction (FGR), defined as being at term and small for gestational age, which underlines the need for reliable indicators of fetal growth.[22] Of the 12 conditions studied, advanced maternal age, BMI lower than 18.5 kg/m^2, hypertension, congenital malformations, and prematurity were more strongly associated with higher adjusted risk of underweight than to stunting or wasting at HA. Prevalence of tuberculosis is three times higher at altitude (53 × 10,000 newborns), and it was only associated with wasting, while nulliparity showed a similar risk for underweight and wasting. No statistically significant evidence of an independent association with any of the phenotypes studied was found for the remaining conditions.

At HA, congenital malformations were associated with duplication of risk of stunting (AOR: 2.62) and wasting (AOR: 2.52), but the risk was seven times higher for underweight (AOR: 7.66).

In the Jujuy Province, and using the same source, Grandi et al.[23] demonstrated that the prevalence of prematurity, SGA, and fetal growth restriction shows an increasing relationship with geographic altitude, where the last two indicators − above 3500 m.a.s.l. − may significantly duplicate the values found at sea level. In Northwestern Argentina, other studies came to the same conclusion,[24] where an increase in prematurity due to an increase in altitude could even represent an adaptive advantage for preterm births under those conditions, as was found in the present study for wasting, with an adjusted risk reduction of almost 40%. Another explanation is that there are three possible alternatives for the presence of an insult that jeopardizes fetal growth under these conditions: gestational continuation, resulting in a newborn with fetal growth restriction; spontaneous or medically indicated interruption of pregnancy, with consequent premature birth; or fetal death.

That background would support the hypothesis that in altitude regions, and by an evolutionary mechanism, prematurity and fetal death may occur because of evident reductions in O_2 tension above 2000 m.a.s.l., suggesting a threshold effect beyond which small reductions in the provision of O_2 may substantially reduce fetal oxygenation.[25] This is sustained by a report of the Argentine Ministry of Health's Bureau of Health Statistics and Information (DEIS), informing that the contribution of premature fetuses ($<37^{+0}$ weeks) to fetal mortality in Jujuy was 72% in 2013.

Geographic altitude and hypertension complications of pregnancy may independently reduce birth weight,[26] a phenomenon found in Jujuy Province newborns above 2000 m.a.s.l.[12,15] and in the current study (Table 1).

Stunting constitutes a global indicator of child welfare, reflecting social inequalities and describing frequent specific results of the neonatal period (low birth weight, small for gestational age, prematurity, short for gestational age and small head circumference). For this reason, the assessment of this indicator in newborns has recently increased in importance in the perspective of the first 1000 days of life. Fetal stunting could be related to organic conditions (e.g. malformations) and is widely regarded as a cumulative, ''long-term'' process analogous to chronic undernutrition in children,[27] that requires exposure to one or more risk factors for several months or throughout pregnancy. Alternatively, neonatal wasting is likely to reflect acute exposures in the weeks before delivery, with more rapid fat deposition.[28] Other studies, however, suggest that differences in severity, rather than the timing and duration of the insults, result in distinct phenotypes of impaired fetal growth, with wasting representing the more severe cases.[29] The fact that phenotype prevalence differs in terms of GA presentation and prevalence between preterm and term pregnancies suggests different risk factors (like diabetes, hypertension or preeclampsia at HA) and consequently, increased medically-indicated interruption of pregnancies to protect maternal and fetal well-being.

Most maternal factors considered in this study were weakly associated with or constitute a protective factor to phenotype differences due to altitude (particularly stunting). Therefore, those differences may probably be attributed to the stressing effect of altitude hypoxia interacting with other characteristics of these ecosystems not considered in this analysis (nutritional, socioeconomic, genetic, ethnic, sociodemographic, and geographic).[10,11,30] The prenatal growth pattern of newborns in the Jujuy Province resembles the pattern found in altitude ecosystems in other ontogenetic stages. In fact, several studies of Jujuy Province children, adolescents and adults' growth indicate that children are shorter and lighter than those living closest to sea level.[10,13] However, since the impaired fetal growth found in the HA population is a complex syndrome, further characterization and validation of phenotypes in different populations is needed.

The main strengths of the study are the high representative sample of geographic altitude, the identification of risk factors of three phenotypes associated with fetal growth restriction knowingly associated with low birth weight, and the introduction of IG-21 as a robust epidemiological tool to be used in future studies.

Limitations

The main limitation is the final sample − 61.2% of live newborns −, probably because only births registered in public facilities were included. Other limitations were incomplete information and GA estimated by the last menstrual date, as recommended by DEIS. On the other hand, models explained low altitudinal risks according to different phenotypes, since factors known to be associated with fetal growth (maternal smoking, use of illicit drugs, history of low birth weight and prematurity, social status, etc.) were not registered.

Conclusions

Underweight, stunting, and wasting risks were higher at a high altitude, and were associated with recognized maternal and fetal conditions. Usage of those three phenotypes will help to prioritize preventive interventions and focus the management of fetal undernutrition.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jped.2018.03.007.

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